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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Samuel D. Bernal

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EXAMINER

EBRAHIM, NABILA G

ART UNIT

PAPER NUMBER

1618

MAIL DATE

DELIVERY MODE

12/23/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/019,494	Applicant(s) BERNAL ET AL.	
	Examiner NABILA G. EBRAHIM	Art Unit 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 11-21 is/are pending in the application.
- 4a) Of the above claim(s) 2 and 11-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 21 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/25/2008 has been entered.

Status of Claims

Claims 1, 2, 11-21 are pending in the application.

Claims 3-10 were previously cancelled.

Claims 2 and 11-20 were withdrawn from consideration.

Claim 21 is new and under restriction for election by original presentation.

Claim 1 is under current examination.

Status of Office Action: Non-Final.

Election/Restrictions

Newly submitted claim 21 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: newly submitted claim 21 is drawn to an independent diagnostic method which can be achieved by performing a biopsy, using a regular or fluorescence microscopy (see for example Johnathan L. et al. Ant malarial Dyes Revisited: Xanthenes, Amines, Examines, and Thiamine's, Antimicrobial agents and Chemotherapy, Dec. 1995, p. 2671–2677. The article is attached to the instant office action). Instant claims are based on a diagnostic method that can be achieved visually by using a visual light.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution

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on the merits. Accordingly, claim 21 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant claims "detecting by visible light during visual examination the retention of said agent by the mitochondria of cancer cells in vivo". The specification does not explain how the step of visual examination that would make the retention of the stain visible by visual examination possible since the mitochondria is a subcellular structure which cannot be seen without an electronic microscope. Thus the specification does not convey to a person having ordinary skill in the art to envisage how the method of visually detecting the retention of the agent by the mitochondria could be achieved.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites "detecting by visible light during visual examination the retention of said agent by the mitochondria of cancer cells in vivo". The mitochondria cannot be seen under

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visible light during visual examination. The mitochondria cannot be seen without a microscope.

Thus the claim is not clear of how to detect the mitochondria during visual examination.

Claim Rejections - 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pomerantz Edwin WO 9726018 (Pomerantz) in view of Oseroff et al., Intramitochondrial Dyes Allow Selective in vitro Photolysis of Carcinoma Cells, PNAS, December 15, 1986, vol. 83, no. 24, 9729-9733 (hereinafter Oseroff) Copyright © 1986 by the National Academy of Sciences and further in view of Brenner, S. et al. Supravital staining of mitochondria with phenosafranin dyes, Biochim et Biophys.1953, pages 11480-11486. (Brenner)

Pomerantz teaches that in-vivo diagnostic procedures for detection of premalignant oral lesions or oral carcinomas, employing dye compositions, which are selectively retained by tissues rendered abnormal due to dysplasia, hyperplasia, tumorigenesis, and other active surface lesions, are known in the art. The reference teaches in vivo detection (corresponds to step b of claim 1) of oral premalignant lesions and oral carcinomas, including the steps of sequentially rinsing (corresponds to step a of claim 1) the oral cavity with a dye stain composition which is selectively retained by cancerous and precancerous tissues, and a rinse composition for removing unretained stain composition, the step of applying to oral tissue, a stain composition comprising a non-toxic dye other than toluidine blue 0 (claim 1). Pomerantz also disclosed that this type of staining is dependent on the dye gaining access to internal subcellular structures such as the nucleus. Such access is readily obtained only by "fixing" a tissue sample of formaldehyde or other reagent that disrupts the

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cellular membrane without destroying general cellular structure (page 2, line 26 bridging to page 3, line 4). Note that it is expected that the mitochondria as a subcellular structure would at least partially absorb the dye. It is also known that the disclosure of oral carcinomas means oral malignancy of epithelial cells recited in instant claim 1.

Pomerantz did not disclose the specific retaining of the mitochondria to the dyes recited in instant claim 1 as amended.

Oseroff teaches that carcinoma cell mitochondria preferentially accumulate and retain cationic dyes to a much greater extent than most normal cells. In addition, Oseroff teaches that rhodamine and cyanine dyes were tested because they can potentially serve as targets for highly selective photochemotherapy. It is noted that alcian blue dye recited by Applicant in amended claim 1 is a cationic cyanine dye.

Oseroff also teaches that the study confirms and extends previous findings that cationic dyes can preferentially accumulate within carcinoma cells and demonstrates that highly selective, light-induced mitochondrial damage and cell killing are possible after brief exposure to some of these dyes. An important aspect of this work is that the photolysis depends only on two relatively "generic" properties mitochondrial accumulation and photosensitization. Thus, though EDKC was the most selective phototoxin in the group of dyes that we evaluated, it is possible that other cationic molecules that concentrate within mitochondria at higher levels or that is more efficient photosensitizers will be still more effective.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a non-toxic dye other than toluidine blue 0 to mark premalignant carcinoma cells as Pomerantz teaches and Oseroff teaches that mitochondria in carcinomatous cells can absorb cationic dyes to a much greater extent than normal cells. Thus the claim would have been obvious because a person of ordinary skill has good reason to pursue the known

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options within his grasp, the skilled artisan would have a good reason in Oseroff's research to navigate among different cationic dyes that can detect oral epithelial carcinoma using the method taught by Pomerantz since it would lead to the anticipated success, it is likely that the results that have been reached are not of innovation but of ordinary skill and common sense.

Thus, Oseroff taught a generic concept of using cationic dyes for early detection of cancers. The reference indicated that it is possible that other cationic molecules that concentrate within mitochondria at higher levels or that is more efficient photosensitizers will be still more effective.

Brenner teaches that phenosafranin dyes supravitaly stains mitochondria (title). The reference teaches that the possibility must be considered that while many basic dyes may adsorb onto isolated mitochondria all do not permeate with equal facility into the living cell. Weakly basic dyes like neutral red penetrate the cell membrane as undissociated bases and stain the vacuoles forming coacervates with ribonucleoprotein. The phenosafranin dyes, however, are completely ionized at neutral pH and would have to penetrate as dye cations (485).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to include phenosafranin in a trial to detect early dysplasia of oral carcinomas because Oseroff motivated people of ordinary skill in the art to try different cationic non-toxic dyes for early detection of cancers. The person of ordinary skill would use the steps suggested by Pomerantz since the reference teaches topical easy method of early detecting oral cancers. The expected result would be a method to detect cancerous cells of the oral epithelium in vivo using cationic non-toxic dyes such as phenosafranin and alcian blue.

Response to Arguments

Applicant's arguments filed 8/25/2008 have been fully considered but they are not persuasive. Applicant argues that:

- Applicant submits that the structure of each of the claimed compounds differs substantially from the structures of those that are disclosed in the cited art, namely Pomerantz and Oseroff. Applicant provide a court case as an evidence that the structure of the compounds of the stains used in staining the cells in the instant claims are different from Pomerantz's and Oseroff.

To respond: In the new amendments to the instant claims crossed out the compounds that are the same as the two references. In addition, the case court provided as an evidence to argue the instant claims against Pomerantz and Oseroff is not relevant because the subject matter of patent 5,045,552 is a compound which structure was recited in claim 1 while instant claims recites a method of using a group of cationic stains to color cells and which many of them were known in the art to have the same effect as disclosed in Pomerantz, Oseroff and Brenner.

- The difference between the structures of what is claimed and that what is disclosed in the prior art is much more different than just a single substitution, i.e., the only difference in Eisai between the structure claimed in the patent-at-issue and the closest prior art is a single substitution at -4. Accordingly, one skilled in the art will appreciate that compounds with different structures are likely to behave differently.

To respond: Applicant is discussing an irrelevant matter of an irrelevant patent as shown in the argument. The subject matter of the discussed patent is a compound and not a method of using a group of different compounds that are used for one purpose as in the instant claims. For example aspirin (acetyl salicylic acid) and Tylenol (acetaminophen) are having totally different structures. However, both drugs have the same effect and are used as analgesics and/or antipyretic. In the instant case, Pomerantz discloses staining compound and ionic derivatives,

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Oseroff teaches that carcinoma cell mitochondria preferentially accumulate and retain cationic dyes to a much greater extent than most normal cells and Brenner teaches that (cationic) phenosafranin dyes supravitaly stains mitochondria. Thus, since Applicant's claims recited different compounds having different structures and since the prior art teaches a generic concept of the cationic dyes to stain epithelial carcinomas, then, it would have been obvious to try different types of cationic non-toxic stains for the same use.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NABILA G. EBRAHIM whose telephone number is (571)272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit
1618